Preliminary Model of Acute Mountain Sickness Severity

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ABSTRACT

Altitude illness severely limits operational effectiveness of dismounted Warriors in mountainous terrains. Commanders, therefore, need accurate estimates and predictors of Acute Mountain Sickness (AMS), the most common altitude illness, to effectively plan and manage missions to altitude.

Purpose

The purpose of this project was to utilize the USARIEM Mountain Medicine relational database (26 studies, 420 subjects, and 91,590 data points) of AMS with relevant subject descriptors and various altitude exposure conditions to develop a preliminary model of AMS severity scores under military-relevant conditions (i.e., rapid ascent, unacclimatized and non-medicated Warriors).

Methods

All volunteers provided descriptive background information and completed an Environmental Symptoms Questionnaire (ESQ). The ESQ assessed AMS severity using the validated AMS-Cerebral (AMS-C) factor score at various time points and elevations. A general linear mixed model was used to model the rate of change in AMS-C scores over time at various altitudes using SAS Proc Mixed (Version 9.1, Cary, NC). Significant covariates were examined in addition to time and the polynomial effects of time and included in the model as necessary. Time was centered at 18 hours.

Results

*The preliminary AMS symptom severity model developed in our laboratory suggests that time^2 ($p=0.006$), altitude ($p=0.0001$), altitude*time ($p=0.009$) and altitude*time^2 ($p=.0001$) are important factors in predicting AMS severity scores. Output from the model suggests that the higher the elevation, the higher the AMS severity scores and that AMS peaks between 16-24 hours of exposure and resolves following 36-40 hours of continuous exposure.*

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14. ABSTRACT
Altitude illness severely limits operational effectiveness of dismounted Warriors in mountainous terrains. Commanders, therefore, need accurate estimates and predictors of Acute Mountain Sickness (AMS), the most common altitude illness, to effectively plan and manage missions to altitude.

15. SUBJECT TERMS

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Conclusion

Although validation of the model is necessary, this is the first model developed using military-relevant conditions which defines the rate of change in AMS severity over time at various altitudes. This preliminary model of AMS is far superior to any currently published estimates of AMS over this altitude range, and can provide quantitative guidance to Commanders in order to develop policy, training and planning tools to sustain Warrior resilience, health and performance at altitude.

1.0 INTRODUCTION

Modern military operations such as those occurring in Afghanistan frequently require rapid deployment of large numbers of personnel into mountainous environments with little or no time for physiological acclimatization. Rapid ascent to high altitude in unacclimatized personnel, however, is a known risk factor for the development of acute mountain sickness (AMS) (4,11). AMS, when severe, can degrade physical and mental performance such that large numbers of troops may be completely incapacitated in their first few days at altitude. One report from Operation Enduring Freedom in Afghanistan indicated that symptoms of altitude illness at moderate (> 1500 m) to high (>3000 m) altitude significantly impacted combat missions (9). Given that the dismounted Warrior is the primary weapon platform in mountainous terrains, Commanders desperately need accurate estimates and predictors of AMS at any given altitude and time point to effectively plan and manage missions

Headache is the cardinal symptom of AMS and is usually accompanied by insomnia, unusual fatigue, dizziness, and nausea or vomiting (11,12). Although the pathophysiology of AMS is not entirely known, available evidence suggests that AMS is due to mild cerebral edema (i.e, brain swelling) caused by the low-pressure atmosphere of altitude. AMS is aggravated by a poor ventilatory response, fluid retention, cerebral vasodilation, and leakage of the blood-brain barrier (5,11). Symptoms of AMS typically become evident 4-12 hours after ascent, peak in intensity in 24-48 hours, and resolve in 2-3 days if no additional gain in altitude takes place (1,5,7,11). The prevalence and severity of AMS symptoms vary with the altitude attained, rate of ascent, length of exposure, previous altitude exposure, and individual susceptibility (4,6,13,15,18). Despite decades of research, no biomathematical model of AMS exists which predicts the rate of change in AMS severity over time at various altitudes following rapid ascent in unacclimatized, non-medicated personnel.

Previous models of AMS cannot be utilized by the military to predict AMS at altitude because they were not developed using a military-relevant scenario (i.e., rapid ascent) or population (i.e, unacclimatized, non-medicated personnel) (15,18,19). Furthermore, conclusions from two of the existing models of AMS were based on a staged ascent to one altitude where AMS was measured at one time point and medication use was largely uncontrolled (15,19). These two models, therefore, provide no information about the dynamic rate of change in AMS severity over time at altitude or the changing degree of AMS severity over a range of altitudes where military personnel may be deployed. Another model of AMS assessed AMS at several time points in order to define the change in AMS severity over time at altitude, but the model utilized an outdated AMS assessment tool and required the previous day assessment of AMS at altitude as a model input (18). Therefore, this model (18) cannot be used prior to deployment to predict AMS severity

The current study addresses limitations of previous AMS models by (1) utilizing the world's largest Mountain Medicine relational database linking altitude ascent profiles with relevant individual descriptors and (2) sophisticated statistical techniques for analyzing longitudinal data. Due to our long history of altitude research using our unique hypobaric chamber and Pikes Peak facilities, our Institute has been able to collect enough AMS data on unacclimatized personnel following rapid ascent to various altitudes under experimentally-controlled conditions over the first few days at altitude to develop a military-relevant predictive model of AMS. In addition, we have employed a new class of statistical models (i.e., general linear mixed model) to investigate the change in AMS severity over time at altitude (16). The basic

characteristic of this model is the inclusion of random subject effects in order to account for the influence of individual subjects on their repeated observations (3). These random subject effects describe each person's starting point and trend across time, and explain the correlational structure of the longitudinal data. This statistical model is quite robust to missing data, irregularly spaced measurements, unbalanced data, violations of constant variance and independence of residuals, and can easily handle both time-varying and time-invariant covariates (16). As such, the general linear mixed model (i.e, random coefficient model) offers several advantages over the typical univariate and multivariate repeated-measures analysis of variance (10,16) for developing a biomathematical model of AMS severity for individuals over time at various altitudes.

The purpose of this project, therefore, was to define a biomathematical model to estimate the rate of change in AMS severity over the first 40 hours of exposure (i.e., highest AMS risk) to various altitudes in non-medicated, unacclimatized personnel following rapid ascent to high altitude (i.e., military relevant scenario).

2.0 METHODS

2.1 Study Population

The study population was pooled from the USARIEM Mountain Medicine Database (26 studies, 420 male and female subjects, 91,590 AMS data points). The final data set included unacclimatized subjects (no altitude exposure > 1000 m in the previous 3 months) following rapid ascent (< 1 h) to various altitudes (1650 m to 4500 m) under experimentally-controlled conditions (no medication use, adequate hydration) over the first 40 hours of altitude exposure (highest AMS risk) to develop a military-relevant predictive model of AMS. After screening for these conditions, 291 males and females (mean±SD; 23.8±5.4 yr, 76.3±12.1 kg, and 1.75 ±0.83 m) were included in the final model. All volunteers received medical examinations, and none had any condition warranting exclusion from the study. Each gave written and verbal acknowledgment of their informed consent and was made aware of their right to withdraw without prejudice at any time. The 26 studies were approved by the Institutional Review Board of the U.S Army Research Institute of Environmental Medicine in Natick, MA. Investigators adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 32 CFR Part 219.

2.2 Altitude Illness Measurements

AMS was assessed at various time points depending on the protocol for each study. In addition to a baseline measurement of AMS at sea level, a minimum of 1 and maximum of 10 repeated measurements of AMS were made per subject at altitude. Given that AMS does not typically develop until 3-6 hours of altitude exposure, only time points > 3 hours were considered in the model. The severity of AMS was determined from information gathered using the Environmental Symptoms Questionnaire (ESQ) (14). The shortened electronic version of the ESQ, which is a self-reported 11-question inventory, is designed to quantify symptoms induced by altitude and other stressful environments (2). Symptom severity is self-rated on a scale of 0-5, with a score of 0 indicating the absence of symptoms and 5 representing the symptom present at maximum intensity. A weighted average of cerebral symptoms (i.e., headache, light-headed, dizzy) was calculated for each volunteer at each AMS assessment and designated AMS-C. An AMS-C score $\geq$ 0.7 was indicative of AMS. The AMS-C scores were natural log-transformed for data analysis to conform to normality assumptions. Zero scores for AMS-C were assigned a random value between 0 and 0.2 in order to perform the natural log transformation.

2.3 Other Covariate

In this preliminary model of AMS-C, altitude was the only covariate utilized as a time-invariant continuous predictor.

2.4 Statistical Analyses

Exploratory data analysis was conducted to determine how individual AMS-C scores changes over time at altitude (i.e, linear, quadratic, cubic, exponential) and also determine likely covariates to include in the model. The cubic effect of time as well as altitude and all interactions with time were included in the initial model. A general linear mixed model (i.e, random coefficient model) was utilized in SAS PROC MIXED (SAS, Cary, NC) to model AMS-C scores over time at various altitudes.

Unconditional means models (i.e, with no covariates) were initially fit for AMS-C scores to ensure that there was significant variation in the data to warrant the inclusion of predictor variables. After determining that there was significant variation in the data, an unconditional growth model for the pattern of change in AMS-C over time (i.e., linear vs. quadratic vs. cubic) was assessed by regressing time, time^2, and time^3 on AMS-C in turn. The intercept, time, time^2, and time^3 were modelled as random effects. If higher orders of time were not significant, they were dropped from the model as both a fixed and random effect and the model was rerun. After determining a suitable individual growth model, level-2 covariates and their interactions with time were included in the model. Non-significant covariates and their interactions with time were eliminated from the model one at a time starting with the least significant effect until the final model was determined. Effectiveness of the time-invariant covariate on explaining between-individual variation in AMS-C scores was assessed using the Pseudo-R^2 statistic (10,16). In addition to the explained variance, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were utilized in selecting the final model using the general guideline of selecting models with lower AIC and BIC values. An unstructured error covariance matrix was used for between-individual random effects in all models. The covariance structure for the within-individual random errors was modelled, if warranted, using a spatial power covariance structure in all models due to the unequal spacing of AMS measurements.

Fundamental diagnostics for two-level mixed models were conducted including examination of residual normality, linearity, homogeneity of variance, and influential outliers. Model diagnostics were utilized to highlight any systematic discrepancies between the data and the fitted model. Plots of residuals against predicted values and every explanatory variable included in the model were examined to detect systematic trends and patterns as well as outliers in the data. A data set for cross-validation of the model has not been collected. The current model, therefore, represents a preliminary model of the rate of change in AMS-C scores over time at altitude. All data analyses were performed with the use of SAS software, version 9.1 (SAS Inc., Cary, NC).

3.0 RESULTS

3.1 Model Specification

The preliminary AMS symptom severity model developed in our laboratory suggests that time^2 (p=0.006), altitude (p=0.0001), altitude*time (p=0.009) and altitude*time^2 (p=.0001) are important factors in predicting AMS severity scores. Time was centered at 18 hours. The final model for AMS-C scores over time at altitude is represented in multi-level form by the following equations:

Level 1 (repeated-measures level) model:

$$\text{Log AMS-C}_{ij} = \beta_{0i} + \beta_{1i}\,(\text{time})_{ij} + \beta_{2i}\,(\text{time}^2)_{ij} + e_{ij} \qquad (1)$$

where i represents the 291 subjects and j represents the different AMS-C measurement occasions. The same model was fit to the 291 subjects separately. Hence, there were 291 different sets of regression coefficients for each subject (i.e., the intercept (β_0), average instantaneous rate of daily change (β_1) and average curvature daily change (β_2). We can summarize these 291 sets of parameter estimates by the following two equations:

Level 2 (individual level) models:

$$\beta_{0i} = \gamma_{00} + \gamma_{01}\,(\text{altitude}_i) + U_{0i} \quad (2)$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}\,(\text{altitude}_i) + U_{1i} \quad (3)$$

$$\beta_{2i} = \gamma_{20} + \gamma_{21}\,(\text{altitude}_i) + U_{2i} \quad (4)$$

The following composite model of AMS-C scores was created by substituting equations (2), (3), and (4) back into equation (1),

$$\text{LogAMSC}_{ij}=\gamma_{00}+\gamma_{01}(\text{altitude}_i)+U_{0i}+((\gamma_{10}+\gamma_{11}(\text{altitude}_i)+U_{1i})*(\text{time}_{ij}))+((\gamma_{20}+\gamma_{21}(\text{altitude}_i)+U_{2i})*(\text{time}_{ij}^2))+e_{ij}$$

U_{0i}, U_{1i}, U_{1i}* time, U_{2i} and U_{2i} * time^2 are the random effects which capture the variation between individual regression models and the average model and e_{ij} represents the variation between individual observations and the regression model within each person.

3.2 Model Output

The unconditional means model indicated that 26.6% of the variability in our AMS-C data was due to differences among individuals that may be explained by including additional covariates in the model. Given the longitudinal nature of the data set (i.e, two or more waves of data per person), the next logical step was the introduction of the predictor time into the level-1 submodel. After exploratory data analysis indicated that most subjects followed a quadratic effect of time, both time and time^2 were introduced into the AMS-C model. By including these predictors, the within subject variation was reduced from 1.303 to model to 0.583 or by 55.3%.

The level 2 variance components quantify the unpredicted variation in the individual growth parameters for the true intercept, true instantaneous rate of change (i.e., time) and true curvature (i.e, time^2) between subjects. The next likely covariate added to the model was altitude. When altitude was added at level 2 in the model, 5.4%, 37.7% and 29.2% of the variability in initial status, instantaneous rates of change, and curvature of AMS-C scores, respectively, were explained. Both the AIC and BIC values were lowest for the model with time, time^2, altitude, altitude*time and altitude*time^2.

Figure 1 represents an example of an AMS-C prediction curve over time at 2500 m, 3500 m, and 4500 m for an unacclimatized, non-medicated Warrior following rapid ascent to altitude. The model demonstrates that the higher the elevation, the higher the AMS severity scores. Importantly, for the same 1000 m increase in altitude at 18 h, AMS severity increases to a much smaller degree from 2500 m to 3500 m than from 3500 m to 4500 m. For instance, the model predicts an AMS-C score of 0.24, 0.57, and 1.34 following 18 hours of altitude exposure at 2500 m, 3500 m, and 4500 m. Each of these numbers represent a 136% increase from the previous number. Similar figures can be developed for other altitudes and timepoints. The model also predicts that AMS peaks following 16-24 hours of exposure and resolves following 36-40 hours of exposure. The exact time point for the peak in AMS severity depends on the altitude but when all altitudes are collapsed, the peak AMS severity occurs after 21.2 hours of exposure.

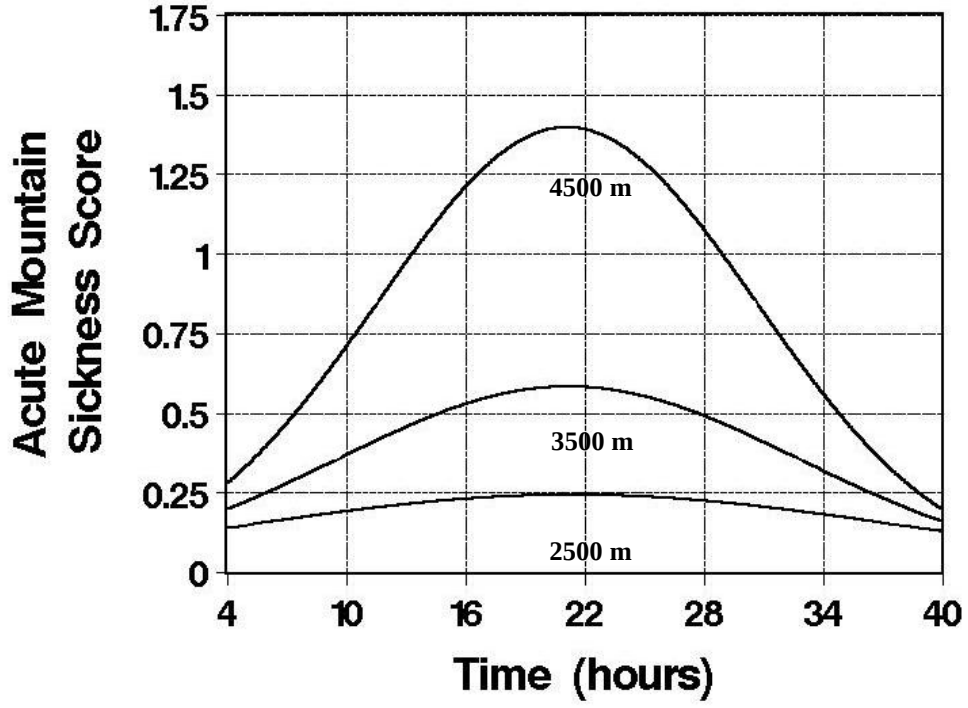

Figure 1: Time Course of Acute Mountain Sickness Scores at Three Different Altitudes.

4.0 DISCUSSION

The major findings from this study are: (1) the higher the altitude, the higher the peak AMS-C severity score, (2) the relationship of AMS-C to a given gain in elevation is not linear, and (3) AMS-C peaks around 16-24 hours of exposure and largely resolves following 36-40 hours of exposure.

This is the first time that a prediction model has defined the rate of change in AMS-C scores over time at various altitudes using a military-relevant scenario. To predict and estimate the rate of change in AMS for individuals by inputting any target altitude, the expected length of time at that altitude prior to deployment represents a huge advancement in the field. Currently, the military depends on "look-up" tables published in technical doctrine to estimate the likelihood and severity of AMS for a given altitude (8). However, the published guidelines are broad and represent population averages with no consideration for individual characteristics. With this current prediction model described here, a Commander can pre-plan a mission at sea-level before altitude deployment to altitude such that important activities occur during the time-frames having the lowest risk of AMS.

While it is well known that the severity of AMS is directly linked to elevation (1,11), quantifying the degree of AMS severity for a given increase in altitude or time at altitude has never been defined with a biomathematical model, as shown in Figure 1. This figure also demonstrates that for a given gain in elevation (i.e., 1000 m) AMS severity is much less going from 2500 m to 3500 m than from 3500 m to 4500 m. The second novel finding from this study is that AMS severity peaks following 16-24 hours of exposure and largely resolves within 36-40 hours of continuous exposure. This finding is different from previously published reports in the literature which suggest that AMS peaks following 24-48 hours of altitude exposure and resolves within 48-72 hours of continuous exposure (1,5,17). The current preliminary model of AMS severity scores suggests that regardless of altitude, peak AMS severity occurs earlier and resolves sooner than previously thought. This model suggests missions at altitude should be planned early upon arrival at the target altitude and that resolution of AMS will occur relatively quickly if the Warrior remains at that elevation.

The next steps in further developing this model include model validation with an independent data set and adding descriptive predictors (i.e, age, height, weight, race, smoking status), physiologic predictors (i.e, heart rate, ventilation, blood pressure), and genomic predictors (i.e, hypoxia-inducible factor 1, angiotensin converting enzyme) to the model to identify individuals at risk for developing AMS. These steps will lead to individualized models of AMS and will greatly improve mission planning capabilities at high altitude

In conclusion, this is the first predictive model to define the rate of change in AMS-C scores over the first 40 hours of altitude exposure in unacclimatized, non-medicated volunteers using a military-relevant scenario. The rate of change in AMS-C scores follows a quadratic function of time and altitude is a significant predictor of AMS-C severity. This preliminary model of AMS severity scores is far superior to any currently published estimates of AMS over this altitude range, and can provide quantitative guidance to Commanders in order to develop policy, training and planning tools to sustain Warrior resilience, health and performance at altitude

5.0 DISCLAIMERS

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